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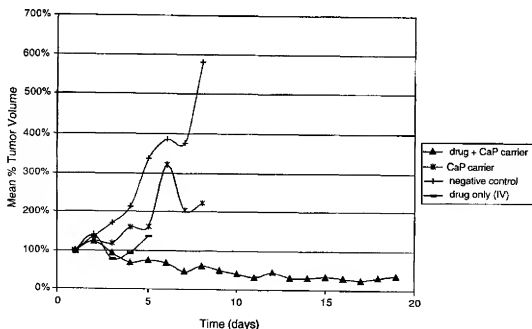
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(54) Title: CHEMOTHERAPEUTIC COMPOSITION USING CALCIUM PHOSPHATE PASTE



(57) Abstract: A method and composition are provided for treating cancer in a mammal. The method includes administering to a tumor site of the mammal an anticancer composition comprising a mixture of an anticancer agent and a calcium phosphate paste, said paste comprised of one or more calcium phosphates and a physiologically acceptable fluid, each calcium phosphate having a Ca/P ratio of less than or equal to 1.7, the paste having an injectable or formable consistency at the time of administration and hardenable at the tumor site.



WO 02/065981 A2



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## CHEMOTHERAPEUTIC COMPOSITION USING CALCIUM PHOSPHATE PASTE

## 5 Background of the Invention

The present invention relates to pharmaceutical compositions and methods for the treatment of cancer.

Following surgical removal or radiation therapy for the removal or reduction of hard and soft tissue tumors, patients are faced with the possibility of persistent tumor cells, metastasis and tumor reoccurrence. In the case of bone tumors, patients face the additional problem of poor mechanical integrity of the bone. Cancer patients typically receive postoperative chemotherapy to reduce the chances of tumor reoccurrence and metastasis. Chemotherapy also is used for the treatment of inoperable tumors. Systemically delivered anticancer drugs often produce severe side effects, such as liver toxicity, cardiotoxicity, hair and weight loss. Therapies often are discontinued or otherwise limited due to these adverse side effects.

While the effectiveness of chemotherapy has improved tremendously, the side effects associated with its administration remain a significant factor in patient mortality. Therefore, an important consideration when treating bone tumors and soft-tissue tumors with chemotherapeutic agents is maintaining a long-acting, yet highly effective concentration of the anticancer agent at the local site of the tumor while minimizing the often toxic systemic side effects.

MacroMed reports the use of a biodegradable polymer having reverse thermal gelation properties for intra-tumoral injections. Under the tradename OncoGel™, the poly(lactide-co-glycolide)-based polymer is deliverable through a small-gauge (25) needle and localized delivery is reported. See, U.S. Patent No. 5,702,717 for further information on the polymeric material.

Hydroxyapatite is a major mineral in bone and teeth. It demonstrates excellent biocompatibility with bony tissue and has been used in the orthopedic industry as bone-filling material. Anticancer agents such as adriamycin, cis-platin and methotrexate have been incorporated into porous hydroxyapatite beads and blocks, and sustained release of the agents have been demonstrated. Administration of the drug-loaded blocks to a tumor site in a cancer rat model resulted in increased life span and reduction in body weight loss. See, Yamamura et al. *Jpn. J. Pharmacol.* 65:289 (1994); Yamamura et al. *Jpn. J. Pharmacol.* 66:433 (1994); and Uchida et al. *J. Orthop. Res.* 10(3):440 (1992).

However, hydroxyapatite ceramics typically are dense, highly crystalline materials, and as such, are poorly resorbable. Porosity must be engineered into the material to permit drug uptake during drug loading and drug release at the tumor site. Engineering of the hydroxyapatite block for a particular drug release profile is difficult and not easily reproducible. An additional limitation of use of a hydroxyapatite solid block or bead is that it requires surgical implantation.

Calcium phosphate cements are compositions having one or more dry components and a liquid which combine to form a material that is capable of setting into a solid calcium phosphate product. Materials that

set into solid calcium phosphate mineral products are of particular interest as such products can closely resemble the mineral phase of natural bone, are potentially remodelable, and are biocompatible.

Patents of interest describing calcium phosphate cements include:

- 5 4,684,673 to Adachi et al.; 5,037,639 to Tung et al., 5,683,461, 5,676,976 and 5,650,176 to Lee et al.; 4,108,690, 5,968,253 to Posner et al. and 5,508,342 to Antonucci et al., as well as 4,880,610, 5,047,031, 5,129,905, 5,336,264, 5,053,212, 5,178,845, and 5,580,623 to Constantz et al.; 5,569,442 and 5,571,493 to Fulmer et al.; and 5,496,399; 5,683,667; 10 5,683,496; and 5,697,981 to Ison et al. Also of interest are WO 96/36562 and WO 97/17285.

- Constantz et al., "Skeletal Repair by in Situ Formation of the Mineral Phase of Bone," *Science* (Mar. 24, 1995) 267: 1796-1798, describes a calcium phosphate cement comprising  $\alpha$ -tricalcium phosphate, 15 monocalcium phosphate monohydrate (MCPM), and  $\text{CaCO}_3$ . Also of interest is Otsuka et al. "A Novel Skeletal Drug Delivery System Using Self-Setting Calcium Phosphate Cement. 9: Effects of the Mixing Solution Volume on Anticancer Drug Release from Homogeneous Drug-loaded Cement" *J. Pharm. Sci.* 84(6):733 (June 1995), which describes a calcium 20 phosphate cement made up of tetracalcium phosphate (TTCP) and dicalcium diphosphate (DCPD) and incorporating the anticancer agent 6-mercaptopurine (6-MP). The addition of 6-MP was reported not to interfere with the setting properties of the cement; however, the drug release profile from the cement was not acceptable, presumably due to 25 crystallization of the calcium phosphate cement with time. The effectiveness of cement as a delivery system was not established, as only model *in vitro* release studies were reported.

A number of these calcium phosphate cements suffer from one or more drawbacks, such as low resorbability, rapid set time, poor flow characteristics and inability to provide controlled release of an active agent. None of the calcium phosphate cements report setting times and  
5 material flow characteristics which are amenable to injection or cannulation.

Thus, there is a need for an anticancer agent delivery system that combines desirable delivery characteristics (e.g. resorbability, controlled release, biocompatibility) in conjunction with the ability to be injectible,  
10 and thus able to administer the therapeutic mixture by syringe or cannula.

There remains a need for a drug delivery system that slowly releases an anticancer agent exclusively into the tumor.

There remains a further need for a drug delivery system that is easy to administer to the tumor site with minimum trauma to the patient.

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### Summary of the Invention

The present invention provides a calcium phosphate composition for use in the local treatment of cancer. The composition demonstrates excellent biocompatibility, controlled drug release and ease of administration. The composition readily incorporates the drug with  
20 simple mixing and can be administered without invasive surgery by injection or by cannula. The setting and crystallization properties of the composition are not significantly affected by the addition of a therapeutic agent.

In one aspect of the invention, a method for treating cancer in a  
25 mammal is provide in which an anticancer composition comprising a mixture of an anticancer agent and a calcium phosphate paste is administered to a tumor site of the mammal. The paste includes one or

more calcium phosphates and a physiologically acceptable fluid, each calcium phosphate having a Ca/P ratio of less than or equal to 1.7. The paste has an injectable or formable consistency at the time of administration and hardenable at the tumor site.

- 5           In one embodiment, the anticancer agent is selected from the group consisting of methotrexate, cis-platin, prednisone, hydroxyprogesterone, medroxyprogesterone acetate, megestrol acetate, diethylstilbestrol, testosterone propionate, fluoxymesterone, vinblastine, vincristine, vindesine, daunorubicin, doxorubicin, hydroxyurea, procarbazine, aminoglutethimide, mechlorethamine, cyclophosphamide, mephalan, uracil mustard, chlorambucil, busulfan, carmustine, lomustine, dacarbazine (DTIC, dimethyltriazenomideazolecarboxamide), fluorouracil, 5-fluorouracil, cytarabine, cytosine arabinoside, mercaptopurine, 6-mercaptopurine, tamoxifen, paclitaxel, etoposide, 15 vinorelbine, gemcitabine, leuprolide, flutamide, goserelin acetate, and thioguanine, and mixtures thereof.

- In another embodiment, the anticancer composition is administered to the tumor site by cannula or by injection, and may be administerable by cannula or injection more than five minutes, preferably more than twenty 20 minutes, after its preparation.

          In some embodiments, the paste hardens into an apatitic calcium phosphate.

- In other embodiments, the calcium phosphate paste includes a calcium phosphate selected from the group consisting of amorphous 25 calcium phosphate, poorly crystalline apatitic (PCA) calcium phosphates (PCA), dicalcium phosphates, such as dicalcium phosphate dihydrate (DCPD) and dicalcium phosphate anhydrous (DCPA), tricalcium phosphates (TCP), monetite, monocalcium phosphate monohydrate

(MCPM), heptacalcium phosphate, calcium pyrophosphate, calcium metaphosphate, octacalcium phosphates (OCP), hydroxyapatites (HA).

- In other embodiments, at least one of the calcium phosphates is selected from the group consisting of amorphous calcium phosphate and
- 5 poorly crystalline apatitic calcium phosphate. One or more calcium phosphates may have a calcium to phosphate ratio in the range of 1.0 to 1.67, or a calcium to phosphate ratio in the range of 1.3 to 1.67. The calcium phosphate paste may have an overall calcium to phosphate ratio in the range of 1.0 to 1.7, or in the range of 1.40 to 1.65.

- 10 In other embodiments, the calcium phosphate paste includes a physiologically acceptable fluid in an amount sufficient to produce a paste having injectable or formable consistency.

- In still other embodiments, a therapeutically effect amount of anticancer agent is released from the composition for a time greater than
- 15 one week, or for a time greater than two week, or for a time greater than one month, or for a time greater than three months.

- In still other embodiments, delivery of the anticancer therapy to the tumor site is sufficient to prevent increase of tumor mass without significant weight loss of the mammal, or delivery of the anticancer
- 20 therapy to the tumor site is sufficient to result in a decrease in tumor mass without significant weight loss in the mammal.

In some embodiments, the particle size of the calcium phosphate is selected to provide a desired release kinetic of the anticancer drug.

- In another aspect of the invention, an anticancer composition is
- 25 provided, which includes a mixture of a physiologically effective amount of an anticancer agent and a calcium phosphate paste. The paste includes one or more calcium phosphates and a physiologically acceptable fluid, each calcium phosphate having a Ca/P ratio of less than or equal to 1.7.



The paste has an injectable or formable consistency at the time of administration and is hardenable at the tumor site.

- In one embodiment, the anticancer agent is selected from the group consisting of methotrexate, cis-platin, prednisone, hydroxyprogesterone, medroxyprogesterone acetate, megestrol acetate, diethylstilbestrol, testosterone propionate, fluoxymesterone, vinblastine, vincristine, vindesine, daunorubicin, doxorubicin, hydroxyurea, procarbazine, aminoglutethimide, mechlorethamine, cyclophosphamide, mephalan, uracil mustard, chlorambucil, busulfan, carmustine, lomustine, dacarbazine (DTIC, dimethyltriazenomideazocarboxamide), fluorouracil, 5-fluorouracil, cytarabine, cytosine arabinoside, mercaptopurine, 6-mercaptopurine, tamoxifen, paclitaxel, etoposide, vinorelbine, gemcitabine, leuprolide, flutamide, goserelin acetate, and thioguanine, and mixtures thereof.

- On another embodiment, the anticancer composition is of a consistency administerable to the tumor site by cannula or by injection.

- In another embodiment, the calcium phosphate cement includes a calcium phosphate selected from the group consisting of amorphous calcium phosphate, poorly crystalline apatitic (PCA) calcium phosphates (PCA), dicalcium phosphates, such as dicalcium phosphate dihydrate (DCPD) and dicalcium phosphate anhydrous (DCPA), tricalcium phosphates (TCP), monetite, monocalcium phosphate monohydrate (MCPM), heptacalcium phosphate, calcium pyrophosphate, calcium metaphosphate, octacalcium phosphates (OCP), hydroxyapatites (HA).

- In other embodiments, at least one of the calcium phosphates is selected from the group consisting of amorphous calcium phosphate and poorly crystalline apatitic calcium phosphate. The one or more calcium phosphates may have a calcium to phosphate ratio in the range of 1.3 to

1.67. The calcium phosphate paste may have an overall calcium to phosphate ratio in the range of 1.0 to 1.7, or in the range of 1.0 to 1.67, or in the range of 1.40 to 1.65.

In still other embodiments, the calcium phosphate paste includes a physiologically acceptable fluid in an amount sufficient to produce a paste having injectable or formable consistency for at least five minutes, or for at least twenty minutes.

In some embodiments, the calcium phosphate paste is hardenable into an apatitic calcium phosphate.

10 In other embodiments, a therapeutically effect amount of anticancer agent is released from the composition for a time greater than one week, or for a time greater than two week, or for a time greater than one month, or for a time greater than three months.

In still other embodiments, delivery of the anticancer therapy to the tumor site is sufficient to at least prevent increase of tumor mass without significant weight loss of the mammal, or delivery of the anticancer therapy to the tumor site is sufficient to prevent a decrease in tumor mass without significant weight loss in the mammal.

20 In some embodiments, the particle size of the calcium phosphate is selected to provide a desired release kinetic of the anticancer drug.

In yet another aspect of the invention, a kit for use in preparing a flowable anticancer composition that remain injectable for at least about 20 minutes includes dry ingredients, such as amorphous calcium phosphate and a second calcium phosphate in a proportion of about 1:10 to 10:1 by weight; a physiologically acceptable aqueous lubricant in an amount sufficient to produce a flowable product upon combination with the dry ingredients; and an anticancer agent in an amount ranging from about 0.01 to 10 wt. % of the dry ingredients.

In one embodiment, the kit may further contain a means of mixing the dry ingredients and the lubricant, or may further contain injecting means.

- By “amorphous calcium phosphate (ACP)” is meant a calcium phosphate solid having significant amorphous character, such as greater than 75%, and preferably greater than 90%, amorphous content. The amorphous calcium phosphate may include localized structure based upon well-known calcium phosphates, such as hydroxyapatite, tricalcium apatite, etc.; however, long-range order is substantially absent. Exemplary ACP materials are found in United States Patent No. 6,117,456, herein incorporated by reference.

- By “poorly crystalline apatitic (PCA) calcium phosphate” is meant a synthetic calcium phosphate of apatitic structure demonstrating only short-range crystallinity. The PCA calcium phosphate is not necessarily restricted to a single calcium phosphate phase, provided it demonstrates the characteristic X-ray diffraction pattern of an apatitic mineral, namely two broad peaks in the region of 20-35° with a peak centered at 26° and a second peak centered at 32°. Exemplary PCA calcium phosphate materials are found in U.S.S.N. 08/729,342.

- By “nanocrystalline calcium phosphate (NCP)” is meant a calcium phosphate solid which exhibits crystalline domains on the order of nanometers or Angstroms. As for ACP, NCP materials may include localized structure based upon well-known calcium phosphates, such as hydroxyapatite, tricalcium apatite, etc.; however, long-range order is substantially absent. Exemplary NCP materials based upon hydroxyapatite are found in United States Patent No. 5,783,217.

### Brief Description of the Drawing

The invention is described with reference to the following drawings which are presented for the purpose of illustration only, which are not intended to be limiting of the invention, and in which:

- 5        Figure 1 is a plot of release of cisplatin over time from sterile (◆) and non-sterile (■) powders of Sample 1;

Figure 2 is a plot of release of cisplatin over time from powders of Sample 1 (both non-sterile) having varying levels of added liquid component;

- 10       Figure 3 shows plots of release of cisplatin over time from NCP powders (Sample 7) (both non-sterile) having varying levels of added liquid component over (A) 140 hours and (B) 25 hours;

- Figure 4 is a plot of the percent change in tumor mass measure *in vivo* over time for athymic nude mice treated with cisplatin in calcium phosphate delivery vehicle of the invention, for rats treated with a positive control (intravenous delivery) and for negative control rats;
- 15       Figure 5 is a plot of total body weight over time for nude athymic mice treated with cisplatin in calcium phosphate delivery vehicle of the invention and for rats treated with a positive control (intratumor injection);

- 20       Figure 6 is a plot of the % tumor mass change over time in C3H mice for 25 mg/kg cisplatin dose in calcium phosphate delivery vehicle (▲), calcium phosphate delivery vehicle alone (\*), no treatment (+), and systemic IV administration of cisplatin (-);

- Figure 7 is a plot of total body weight over time for C3H mice
- 25       treated with cisplatin in calcium phosphate delivery vehicle of the invention (◆), and for rats treated with a positive control (intravenous administration) (■);

Figure 8 is a plot of the % tumor mass change over time for C3H mice for 25 mg/kg cisplatin dose in calcium phosphate delivery vehicle (▲), calcium phosphate delivery vehicle alone (\*), no treatment (+), and systemic IV administration of cisplatin (-); and

- 5        Figure 9 is a plot of total body weight over time for C3H mice treated with cisplatin in calcium phosphate delivery vehicle of the invention (◆), and for rats treated with a positive control (intravenous administration) (■).

#### Description of the Preferred Embodiments

- 10        The calcium phosphate composition of the invention demonstrates excellent biocompatibility, controlled drug release and ease of administration. The composition readily incorporates the drug with simple mixing and can be administered without invasive surgery by injection or by cannula. The flowable material may be injected into a
- 15        cancellous bone void and the material sets into a solid calcium phosphate product that is capable of withstanding physiological loads, making such products extremely attractive for use in the treatment of bone tumors. The composition may similarly be injected into soft-tissue tumors. The flowable nature of the calcium phosphate composition of the invention
- 20        allows the mixture to flow around and into the tumor, where it hardens into a calcium phosphate cement. The tumor may be encapsulated thereby in the hardened calcium phosphate cement which confines the cancer cells of the tumor and helps to prevent metastasis.

- The calcium phosphate paste may include any calcium phosphate
- 25        material in which the chemical composition and material properties have been selected to provide the desired flow properties and bioresorption. The desired flow properties include the ability to deliver the calcium

phosphate composition by syringe or cannula. The paste is considered "injectable" if it is capable of passing through a 16 gauge needle. In preferred embodiments, injectability is maintained after storage, for example, for one minute, five minutes, ten minutes and most preferably 30 minutes. Injectability is evaluated by determining the ability to inject 1 cc of paste material through a 16 gauge needle or smaller, with only finger or hand pressure being applied by the user. The material is capable of injection through small gauge needles, e.g., 18-gauge to 25-gauge needles.

The paste is made up of a dry powder component, a liquid component and an anticancer agent.

The dry component includes one or more calcium phosphates. Each calcium phosphate has a calcium to phosphate (Ca/P) ratio of less than or equal to 1.7, and preferably a Ca/P ratio in the range of 1.0-1.65. Calcium phosphates of interest include, but are not limited to, calcium phosphates such as amorphous calcium phosphates (ACP), poorly crystalline apatitic (PCA) calcium phosphates (PCA), dicalcium phosphates, such as dicalcium phosphate dihydrate (DCPD) and dicalcium phosphate anhydrous (DCPA), tricalcium phosphates (e.g.,  $\alpha$ - and  $\beta$ -TCPs), monetite, monocalcium phosphate monohydrate (MCPM), heptacalcium phosphates, calcium pyrophosphates, calcium metaphosphates, octacalcium phosphates (OCP), hydroxyapatites (HA). Other calcium phosphates are described by Driessen (1995), which is hereby incorporated by reference. Carbonated or otherwise substituted versions of these calcium phosphates are also contemplated in the invention. Calcium deficient or poorly crystalline apatitic calcium phosphates having a Ca/P ratio of about 1.0-1.65, preferably 1.0-1.6, or 1.0-1.5 or 1.0-1.4, or 1.50-1.65, and more particularly 1.55-1.65, are preferred. Another preferred calcium phosphate is amorphous calcium

phosphate (ACP), in particular, ACPs having a Ca/P ratio of about 1.3 to 1.67, and preferably 1.3-1.6, or 1.4-1.55 or more preferably 1.4-1.5. Yet another preferred calcium phosphate is nanocrystalline calcium phosphate (NCP), in particular a hydroxyapatitic NCP.

- 5       The preferred calcium phosphates, ACP, NCP or PCA calcium phosphate, may be alone, or in combination with each other, or individually with a second calcium phosphate to form the dry component of the composition. Suitable second calcium phosphates are those which are capable of reacting with the primary calcium phosphate to form a
- 10 hardened cement. Exemplary calcium phosphates include dicalcium phosphates, such as dicalcium phosphate dihydrate (DCPD) and dicalcium phosphate anhydrous (DCPA), tricalcium phosphates (TCP), monetite, monocalcium phosphate monohydrate (MCPM), heptacalcium phosphate, calcium pyrophosphate, calcium metaphosphate, octacalcium phosphates
- 15 (OCP), hydroxyapatites (HA). A preferred dry powder combination is an amorphous calcium phosphate and dicalcium phosphate, e.g., DCPD. Another preferred embodiment is a poorly crystalline apatitic calcium phosphate and a dicalcium phosphate. In yet another preferred embodiment, a nanocrystalline calcium phosphate is employed. A
- 20 detailed description of the preparation and characteristics of suitable calcium phosphates can be found in U.S. Patents 5,683,461, 5,783,217 and 6,117,456, which are hereby incorporated by reference.

A particularly preferred dry component is a combination of calcium phosphate powders which react to form an apatitic calcium phosphate.

- 25 Hydroxy apatite is the mineral component of naturally-occurring bone having a Ca/P ratio of 1.67, although the actual Ca/P ratio of bone varies between 1.5 and 1.7. The composition and relative amounts of the dry powder components preferably are selected to provide an overall Ca/P

ratio in the range of 1.0-1.7, or 1.3-1.65, or 1.4-1.6, or preferably close to that of naturally-occurring bone, that is in the range of 1.45 to 1.7. It has been observed that calcium-deficient compositions exhibit more rapid, resorption characteristics. In some embodiments where rapid resorption is  
5 desired, it may be desired to use select dry powder components to provide an overall Ca/P ratio of less than 1.67, and preferably in the range of 1.4 to 1.65.

The composition of the invention also includes one or more anticancer agents. The anticancer agent may be introduced with the  
10 powder component, or with the liquid component of the composition, or it may be separately added to the composition. Suitable anticancer agents may be one or more of known chemotherapy drugs such as methotrexate, cis-platin, prednisone, hydroxyprogesterone, medroxyprogesterone acetate, megestrol acetate, diethylstilbestrol, testosterone propionate,  
15 fluoxymesterone, vinblastine, vincristine, vindesine, daunorubicin, doxorubicin, hydroxyurea, procarbazine, aminoglutethimide, mechlorethamine, cyclophosphamide, mephalan, uracil mustard, chlorambucil, busulfan, carmustine, lomustine, dacarbazine (DTIC, dimethyltriazenomideazolecarboxamide), fluorouracil, 5-fluorouracil,  
20 cytarabine, cytosine arabinoside, mercaptopurine, 6-mercaptopurine, tamoxifen, paclitaxel, etoposide, vinorelbine, gemcitabine, leuprolide, flutamide, goserelin acetate, and thioguanine, and mixtures thereof.

Exemplary anticancer agents and the suggested dosage are found in Table 1. The amount of anticancer agent that is present in the cement will  
25 be sufficient to provide a composition that at least prevents tumor growth in the region where the composition has been introduced as compared to a



control. In preferred embodiments, the amount and effectiveness of the anticancer agent is sufficient to reduce the tumor size or even to substantially eliminate the tumor.

Table 1.

Cancer	Drug	Mechanism of action	Dosage	response rate
Breast	tamoxifen	non-steroidal antiestrogen; inhibits binding of estrogen to receptors	20mg/daily (tablet)	as 1 <sup>st</sup> line hormonal therapy; 60% steroid receptor cancers respond
	doxorubicin	inhibits action of topoisomerase II; forms free radicals, binds to membrane	60-75 mg/m <sup>2</sup> IV (every 21 days)	none known
	methotrexate	inhibitor of dihydrofolate reductase; interferes with cellular enzymes	30-40 mg/m <sup>2</sup> IV (once a week)	with cyclophosphamide and 5-fluorouracil, 30-50%)
	cyclophosphamide	alkylating agent; crosslinks DNA and RNA strands, prevents cell division	50-1000 mg/m <sup>2</sup> , 1x treatment	35% alone, 90% combination therapy
	5-fluorouracil	effects DNA and RNA	500 mg/m <sup>2</sup> , 1x/day, repeat 4-5 wk	partial remission 10-20%
	paclitaxol	stabilizes microtubule formation leading to cell death	175 mg/m <sup>2</sup> , (every three weeks)	56-62% response in previously treated patients
small cell lung	etoposide (+ cisplatin)	interferes with DNA synthesis by interacting with topoisomerases II	80 /m <sup>2</sup> for three days	30-35% alone; 50% with cisplatin
non-small cell lung	paclitaxol (+ cisplatin)	interferes with DNA synthesis by interacting with topoisomerases II	80 mg/m <sup>2</sup> for three days	mg34-40% in previously untreated patients
	vinorelbine (+ cisplatin)	antitubulin, causes mitotic arrest in G2 and M phases	30 mg/m <sup>2</sup> for 3 days	33% alone; 28% with cisplatin
	gemcitabine (+ cisplatin)	affects cell undergoing DNA syntheses and blocks progression through G1/S	not given in lungs	not given in lungs

prostate	leuprolide	desensitizes LH-RH receptors and reduces release of hormones	7.5 mg im, 1X month	survival favored for leuprolide/flutamide combination
	goserelin acetate	downregulates LH-RH receptor, medical castration, reduces testosterone	3.6 mg s.c., 1x month	with flutamide 70%
	flutamide	nonsteroid antiandrogen, used with LH-RH analogue	250 mg, every 8 h, orally	70% combination therapy
	diethylestilbestrol	synthetic estrogen	1-3 mg, daily	65%

In other embodiments, two or more anticancer agents are included in the composition. Certain combination therapies have been identified as particularly effective and are found in Table 2. The amount of anticancer agent that is present in the cement will generally range from about 0.01 to 10, usually from about 0.01 to 5.0 and more usually from about 0.01 to 3.0% by weight of the dry ingredients of the cement.

Table 2.

Cancer	combination therapy
breast	5-fluorouracil, doxorubicin ( $> 60 \text{ mg/m}^2$ ), cyclophosphamide
	cyclophosphamide, doxorubicin ( $< 60 \text{ mg/m}^2$ ), 5-fluorouracil
	cyclophosphamide, methotrexate, 5-fluorouracil
	doxorubicin, paclitaxol
small cell lung	cisplatin, etoposide
non-small cell lung	cisplatin, paclitaxol
	cisplatin, vinorelbine
	cisplatin, gemcitabin
prostate	leuprolide, flutamide
	gosereline acetate, flutamide

Also provided are kits comprising the subject chemotherapeutic delivery vehicle, where the dry and liquid components may be present in separate containers in the kit, or some of the components may be combined into one container, such as a kit wherein the dry calcium phosphate components are present in a first container and the liquid components are present in a second container. Instructions for use may also be included. The kit preferably includes dry ingredients comprising amorphous calcium phosphate, nanocrystalline or PCA calcium phosphate and a second calcium phosphate in a proportion of about 1:10 to 10:1 by weight, and preferably about 50:50 by weight; a physiologically acceptable aqueous lubricant (liquid component) in an amount sufficient to produce a flowable product upon combination with the dry ingredients; and an anticancer agent in an amount sufficient to produce the desired pharmaceutical effect and typically ranging from about 0.01 to 10 wt. %

of the dry ingredients. Due to the need to carefully titrate the amount of anti-cancer agent based upon patient body mass and tumor size, the agent may be added separately. The agent may be added to the liquid component prior to mixing with the dry component, or it may be added to the injectable paste, once formed.

In preparing the subject calcium phosphate cements for use in the treatment of cancer, the dry components and the liquid components will be combined using any suitable means to produce a homogeneous, flowable paste-like material having the characteristics described above. One suitable means of combining the dry and liquid components is a mortar and pestle, with which the liquid and solid components are mixed to produce the flowable paste. Alternatively, one may employ an automated mixing device. See, United States Patent No. 5,980,482, hereby incorporated by reference, for further description of a suitable mixing device.

Generally, the calcium phosphate composition is formed into an injectable gel or solid nanoparticle paste by the addition of a liquid component or lubricant. The liquid component is a physiologically acceptable liquid, such as but not limited to, water, saline, sodium phosphates, buffer solutions, serum, or tissue culture media. The liquid component may include one or more solutes, selected to buffer the liquid, stabilize the anti-cancer agent, or otherwise modify the properties of the calcium phosphate composition, e.g., modify reaction and hardening times or modify the composition or crystallinity of the product calcium phosphate. For example, sodium phosphate is typically used to accelerate the hardening of the calcium phosphate paste. The preferred calcium phosphate paste may be designed to absorb, bind, entrap or otherwise contain the anticancer agent. The calcium phosphate cements, paste-like

compositions and products are combined with an anticancer agent for its local delivery to a physiological site of interest. The calcium phosphate paste containing the anticancer agent remains formable and injectable at room temperature, facilitating the administration of the composition to a  
5 tumor site by injection or by cannula.

The calcium phosphate cement may be selected to set rapidly or slowly at room temperatures. In many instances it will be advantageous to have the calcium phosphate paste set slowly at room temperature, for example, to allow the medical professional adequate time to administer the  
10 therapeutic composition to the tumor site. For example, the calcium phosphate paste may remain flowable and injectable at room temperatures for a significant time, e.g., more than 5 minutes, more than 10 minutes, more than 20 minutes, and up to an hour. The calcium phosphate paste should nonetheless set rapidly under physiological conditions, e.g., less  
15 than 20 minutes, less than 10 minutes and preferably within 5 minutes. Thus, preferred calcium phosphate compositions exhibit a "dual setting" characteristic in that they are slow to set at about room temperature, e.g., 20-25 °C, yet set rapidly at physiological temperatures e.g., 35-40 °C. In such instances, a composition including PCA calcium phosphate or  
20 amorphous calcium phosphate as one of the components may be used.

In those instances where a more rapidly setting cement is desired, accelerators may be added to the composition. Exemplary accelerators include water-soluble sodium salts, such as sodium phosphate, sodium succinate, sodium lactate, sodium chloride, sodium acetate and the like.

25 Setting times may be determined using well-established standards, such as the Gillmore needle test (ASTM C 266-89 Standard Test Method of Time of Setting of Hydrulic-Cement Paste by Gillmore Needles) and the needle penetration test C 403/C 403M-95 Standard Test Method for

Time of Setting of Concrete Mixtures by Penetration Resistance. The effect of the anticancer agent on the setting times may be determined using these tests as well.

- Once in place, the paste hardens and releases the anticancer agent
- 5 into the tumor environment over an extended period of time, relying on a combination of drug solubility and bioerosion of the calcium phosphate delivery vehicle. The calcium phosphate composition may be formulated to be resorbable over a preselected period of time. Calcium phosphate cements may be prepared which resorb within at least about 1 week,
- 10 within about one month, within about one month and preferably within a year, so that the calcium phosphate cement may release the anticancer agent into their local environment for as long as is needed, depending on the specific cement from which the composition is prepared. Thus, the subject compositions find use as anticancer agent delivery vehicles, i.e. as
- 15 anticancer agent depots, in which the local delivery of an anticancer agent for an extended period of time is desired. The subject compositions find particular use as local anticancer agent delivery vehicles for bone tissue, particularly cancellous bone tissue.

- In most cases, the anticancer compositions are resorbable.
- 20 Resorbable calcium phosphate cements biodegrade over time, ultimately leaving little or no residual material in the body. Resorbability generally eliminates the need for surgical removal of the delivery vehicle, after completion of chemotherapy. Resorbable calcium phosphate cements also allow the controlled delivery of active agents to a the tumor site at a
- 25 specific rate. The anticancer agent typically is delivered to a tumor site at a rate comparable to the resorption rate. Custom designed resorbability characteristics of the anticancer composition provides for selected delivery rates. In preferred embodiments, weakly resorbing calcium phosphate

cements will be used to provide a slow release delivery of the anticancer agent to the tumor site. In other embodiments, the calcium phosphate cement will be strongly resorbable and provide a means to deliver a fast, quick dose of the anticancer agent to the tumor site. In yet other  
5       embodiments, a combination of weakly and strongly resorbable calcium phosphates will be used to produce a variable or pulsatile kinetic release. The resorption rate, and therefore the delivery rate, can be adjusted to hours, days, weeks, months, and even years by varying the preparations of the variously resorbing components.

10       A strongly resorbing calcium phosphate is characterized as follows: when at least 0.1 gram (preferably 0.1-0.5 g) is implanted in an osseous, subcutaneous or intramuscular site, at least 80% of the material is resorbed within one year. In more preferred embodiments, 0.5 gram of the calcium phosphate will be resorbed within nine months, six months, three months,  
15       and ideally one month or less, depending of the desired delivery profile desired at the tumor site. Weakly resorbable means that less than 80% of 0.1 gram of starting calcium phosphate is resorbed after one year. Resorption, as used herein, encompasses solubility based dissolution processes, as well as active cellular or enzyme based processes. Preferred  
20       materials are resorbed through active cellular or enzymatic processes. By controlling the rate of active degradation of the calcium phosphate cement, the inventive calcium phosphate cements can be tailored to have linear resorption rates, and can be tailored to avoid initial high concentration spikes where undesirable.

25       Resorbability of the calcium phosphate vehicles also may be varied through the adjustment of one or more physical parameters including vehicle size, vehicle particle size, porosity, density, and/or crystallinity. For example, monolithic devices, on the order of one gram will resorb

more slowly than one gram of the same material when in particulate form. Two or more of these parameters will generally be adjusted in concert to fine-tune the final resorption rate.

For precipitated calcium phosphates, particle sizes may be  
5 controlled by careful control of the precipitation rate. Rapid precipitation, followed by rapid harvesting of the precipitate, is useful in the production of small particle sizes (e.g. particle size ranging from 5 nm to 150 nm) of low crystallinity. The use of standard milling processes known to the art (e.g. ball mills, roller mills, jet mills) followed by precise sieving, will also  
10 be useful in preparing vehicles of specific size particles. In other instances materials prepared from slurries, as described in the art, will produce useful particle size materials. Particle sizes of less than 1 mm, preferably less than 0.5 mm, are generally preferred for delivery vehicles intended to be resorbed within six months.

15 Cements can be induced to form particulates during hardening through the use of an emulsifying agent and injection of the cement as an emulsion. Emulsifying agents will be solubilized from the hardened material leaving a macropore matrix. Suitable emulsifying agents include lethicin, dimethicone, and the like.

20 Density of the hardened calcium phosphate composition also has a significant effect on resorption rates. Different calcium phosphate compositions result in different density and grain sizes. Higher density or larger grain size, of course, reduce resorption rates. Leachable or biodegradable materials may be incorporated into the paste that may be  
25 subsequently removed *in vivo*, e.g., by dissolution or cellular action, so that a porous vehicle results. Suitable additives should of course be biocompatible and physiologically acceptable at the doses required to induce porosity. Other methods of affecting calcium phosphate density



are discussed in Driessens et al. in Encyclopedic Handbook of Biomaterials and Bioengineering, Chapter 31, "Calcium Phosphate Bone Cements", Wise (Ed.), Marcel Dekker (1995).

- Control of the calcium phosphate cement degree of crystallinity and
- 5 crystal size may be used to affect the overall vehicle resorption rate. For apatitic calcium phosphates with calcium to phosphorous ratios of 1.3-1.75, poorly crystalline forms are believed to resorb more quickly than highly crystalline forms. Highly crystalline stoichiometric hydroxyapatite (e.g. NIST catalog # 2910) is an example of a weakly or even non-
- 10 resorbable vehicle. For other calcium phosphates, for a given calcium to phosphorous ratio, more amorphous forms will generally be more soluble than more crystalline forms. Increased resorption rates may be achieved through the production of apatitic calcium phosphates containing lattice defects, such as ionic vacancies or substitutions. Preferred embodiments
- 15 include carbonated or otherwise calcium deficient apatites, i.e.,  $\text{Ca/P} < 1.67$ , all of which tend to have increased *in vivo* resorption rates.

- Selection of the particular calcium phosphates may be made to provide a desired resorption rate in the device. For example, it has been found that calcium phosphate cements prepared with amorphous calcium
- 20 phosphate, and in particular with amorphous calcium phosphate and dicalcium phosphate dihydrate, resorb rapidly, e.g., over the course of 3-4 weeks in a subcutaneous site. In comparison in a comparable *in vivo* site, calcium phosphate cements prepared with nanocrystalline calcium phosphate, and in particular with nanocrystalline calcium phosphate and
- 25 dicalcium phosphate dihydrate, resorb much more slowly, e.g., over the course of more than one month. Each type of calcium phosphate cement may be preferred in specific therapeutic settings.

Further guidance for the production of similar such apatitic calcium phosphates can be found in Structure and Chemistry of the Apatites and Other Calcium Orthophosphates, (Elsevier, Amsterdam, 1994, by J.C. Elliott), and the references contained therein, all incorporated herein by  
5 reference.

The inventive delivery vehicle can be of any porosity that provides the desirable characteristics for anticancer drug delivery. Porosity facilitates both the diffusion of substances to and from the inventive material and, in certain applications, the penetration of cells and cell  
10 processes into the material matrix. Accordingly, calcium phosphate cements of lower porosity tend to resorb more slowly in vivo than those of higher porosity; therefore, the greater the porosity, the greater the rate of resorption. In one embodiment of the invention, porosity is increased through the use of a dry mixture of controlled particle size reactants. For  
15 example, a reactant with a larger particle size (e.g. 300-500  $\mu\text{m}$ ) will produce a more porous material. Soluble porogens may also be used to control the porosity of the calcium phosphate material.

Additionally, certain molecular factors may be incorporated into the vehicle that can be used to affect its resorption rate by influencing the  
20 cellular or enzymatic processes that ordinarily mediate vehicle resorption in the body. These incorporated factors are often biologically active molecules or collections thereof, which affect bone metabolic processes, such as the activity of osteoclasts and/or osteoblasts. In other instances the incorporated factors attract or otherwise affect the activity of one or  
25 more of macrophages, monocytes, or foreign body giant cells. Such useful factors include: growth factors, enzyme inhibitors, extracellular matrix components, cytokines and the like.

- Incorporation of factors, which attract or inhibit osteogenic cells and/or macrophages, can have a significant effect on calcium phosphate cement resorption rate. Thus, incorporation of bone morphogenetic protein into the inventive calcium phosphate cements will lead to more rapid resorption of the vehicle, particularly in soft tissue implant sites. Additionally, factors that attract osteoclasts (e.g. interleukin-1, lymphotoxin, calcitonin, ) may be used to promote degradation of the vehicle. Osteoclast or macrophage activity inhibitors (e.g. neutral phosphate, glucocorticoids, plicamycin, gallium nitrate) may be used to prolong the resorption process. Extracellular matrix components, such as laminin, RDG peptides, collagen, fibronectin may also be included with the calcium phosphate cements. Further guidance regarding specific factors useful in the regulation of calcium phosphate resorption rates can be found in PCT/US97/18528, incorporated by reference herein.
- Generally, these factors will be incorporated into the inventive calcium phosphate cements as a concentration of less than 20% wt/wt preferably less than 10% and in most embodiments, less than 5%.

- In many instances, calcium phosphate cement resorbability is preferred; however, it is not always required or desired. In some embodiments, a calcium phosphate cement that is either weakly resorbable or substantially non-resorbable may be used. A non-resorbable calcium phosphate cement may be used when prolonged chemotherapy is required over a matter of several years. A non-resorbable calcium phosphate cement may also be desirable in cases when the calcium phosphate cement is used additionally as a support matrix for tissue repair or growth, as a treatment for a disease. Non-resorbable calcium phosphate calcium phosphate cements can remain in the body without detrimental effects to the host due to their excellent biocompatibility. Alternatively,

non-resorbable calcium phosphate cements may be surgically removed following the desired delivery period. Suitable non-resorbable or weakly resorbable calcium phosphate cements include those prepared from sintered hydroxyapatite.

- 5           Ultimately, resorption rates may be established empirically by using intramuscular or subcutaneous implantation of the calcium phosphate cement in one or more small animal models to assess the exact effect of formulation adjustments on calcium phosphate cement resorption rates. In these model systems, a variety of candidate formulations may be tested simultaneously and resorption rates can be compared at various  
10           time points using standard histological, radiographic or other methods known to the art.

- The calcium phosphate paste may also be formulated in a manner which enhances its receptiveness to the cancer cells. For example, the pH  
15           of the delivery vehicle may be tailored to be particularly receptive to cancer cells. Cancer cells typically produce an environment that is of lower pH (more acidic) than that associated with healthy host cells. The composition of the calcium phosphate paste may be selected to provide a resultant hardened calcium phosphate having a pH which enhances the  
20           effectiveness of the anticancer therapy. Practitioners of calcium phosphate chemistry will know to use those calcium phosphates having the least solubility (for longer release times) at the expected pH at physiological temperatures. In most embodiments, the composition is selected for pH stability at neutrality or under slightly acidic conditions.
- 25           Guidance for preparations of calcium phosphate cements of differing pHs can be found in the solubility isotherm data such as that provided by Brown in "Phase relationships in the ternary system  $\text{CaO-P}_2\text{O}_5\text{-H}_2\text{O}$  at 25 C," *Amer. Ceram. Soc.* 75:17 (1992) and by J.C. Elliot in "Structure and

Chemistry of the Apatites and Other Calcium Orthophosphates," *supra*.

The invention also provides a method for the treatment of cancer. The method includes administering an anticancer composition to a tumor site of a patient. The anticancer composition includes a mixture of an anticancer agent in a calcium phosphate paste delivery vehicle. The paste is made up of two or more calcium phosphates and a physiologically acceptable fluid, each calcium phosphate having a Ca/P ratio of less than or equal to 1.7. The paste is injectable or formable at the time of administration which allows the paste to be introduced directly at and into the tumor. The paste then hardens rapidly at the tumor site.

The method of the invention has been investigated for the treatment of breast and prostate cancer, although the methods and compositions described herein may be readily adapted for the treatment of many kinds of cancer.

Example 1. This example describes the preparation of an amorphous calcium phosphate (ACP) gel for use in a drug delivery preparation for delivery of a chemotherapeutic.

Solution A was prepared at room temperature by the rapid dissolution of 55g  $\text{Na}_2\text{HPO}_4 \cdot 7\text{H}_2\text{O}$ ; 50g NaOH; 30g  $\text{NaHCO}_3$  in 1.3 liters of distilled water. Solution B was prepared at room temperature by rapid dissolution of 43g  $\text{Ca}(\text{NO}_3)_2 \cdot 4\text{H}_2\text{O}$  in 0.5 liters of distilled water.

Carbonated amorphous calcium phosphate was then prepared at room temperature by the rapid addition of solution B to rapidly stirring solution A. The precipitate of gel-like amorphous calcium phosphate thus formed was aged or allowed to stand at room temperature for approximately 30 seconds. After aging, the precipitate was filtered using filter paper ( $0.05 \text{ m}^2$ ) with medium filter speed and a vacuum pressure of about  $10^{-2}$  torr. The precipitate formed a thin cake and was washed with

approximately 4 liters of distilled water by adding water into the filtrating funnel. The gel pH was measured using a pH probe and determined to be pH 13.5.

- Example 2. This example describes the preparation of an
- 5 amorphous calcium phosphate (ACP) powder for use in a drug delivery preparation for delivery of a chemotherapeutic.

An ACP gel was prepared according to example 1, but with the modification that the precipitate was aged or allowed to stand at room temperature for 5 minutes. The washed material was then collected using a

10 spatula and immersed into a liquid nitrogen in a 2.5 L container. Following the formation of hard frozen pieces, the container was transferred into a vacuum chamber for 24 hours ( $10^{-1}$  -  $10^{-2}$  torr), until a fine and dry powder was obtained.

- Example 3. This example illustrates the typical formation of a
- 15 nanocrystalline calcium phosphate (NCP) gel for use in a drug delivery preparation for delivery of a chemotherapeutic.

A solution of 218 g of disodium  $\text{Na}_2\text{HPO}_4 \cdot 12 \text{H}_2\text{O}$  in 1.2 liters of distilled water and a solution of 70 g of  $\text{Ca}(\text{NO}_3)_2 \cdot 4\text{H}_2\text{O}$  in 0.5 liters of distilled water were prepared. The calcium solution was quickly poured

20 into the phosphate solution at room temperature with stirring. Precipitation was immediate and substantially complete. The precipitate was adjusted to pH 6.4 by the addition of sodium hydroxide solution in order to avoid the formation of acidic calcium phosphates. The precipitate was aged at room temperature for 5 minutes prior to filtration. The

25 precipitate was then filtered through a Buchner filter (with a total surface about  $0.1 \text{ m}^2$ ), and was washed by about 3 liters of distilled water. A gel cake of nanocrystalline calcium phosphate obtained on the filter paper.

Example 4. This example illustrates the typical formation of a nanocrystalline calcium phosphate (NCP) powder for use in a drug delivery preparation for delivery of a chemotherapeutic.

The calcium phosphate apatite material was prepared according to example 3 but with the following modifications. The washed precipitate was collected using a spatula and immersed into liquid nitrogen in a 2.5 L container. Following freezing, the container was transferred into a vacuum chamber for 24 hours ( $10^{-1}$  -  $10^{-2}$  torr), until a fine and dry powder was obtained.

Example 5. This example illustrates the preparation of an apatitic calcium phosphate drug delivery agent for delivery of a chemotherapeutic.

Dicalcium phosphate dihydrate (DCPD) was prepared at room temperature by the rapid addition of solution B (17.1 g  $\text{Ca}(\text{NO}_3)_2 \cdot 4\text{H}_2\text{O}$ ; 0.250 liters distilled water; pH 5.5-6.0 to a stirred solution A (10 g  $\text{H}_2\text{N}_2\text{O}_4\text{P}$ ; 0.5 liters distilled water; pH 7.8). Immediately thereafter, the sample was filtered using filter paper (0.05 sq. m) with medium filter speed and a vacuum pressure of about  $10^{-2}$  torr. The material formed a thin cake which was washed with about 2 liters of distilled water and then dried at room temperature for 24-72 hours.

Amorphous calcium phosphate was prepared according to example 1. The washed material was then collected using a spatula and immersed into a liquid nitrogen in a 2.5 L container. Following freezing, the material was transferred into a vacuum chamber for 24 hours ( $10^{-1}$  -  $10^{-2}$  torr), until a fine and dry powder was obtained. The material was then heated for 80 minutes at  $455^\circ\text{C}$  ( $\pm 3^\circ\text{C}$ ).

The reactive amorphous calcium phosphate material was physically dry-mixed with  $\text{CaHPO}_4 \cdot 2\text{H}_2\text{O}$  at 50:50 weight percent using a mortar and pestle for 3-5 minutes. Water (1 ml/g of mixed material) was then added

to the powder mixture to yield a hydrated precursor of paste-like consistency. The amount of  $H_2O$  added varied, depending on whether a thick or thin paste was desired. The paste material was then placed in a moist tissue environment where upon reaching body temperature ( $37^\circ C$ ), it hardened into a solid mass. The hardening process could be delayed for several hours by placing it into a refrigerating temperature of  $4^\circ C$ .

Example 6. This example illustrates the preparation of an apatitic calcium phosphate drug delivery agent for delivery of a chemotherapeutic using NCP powder.

- 10 NCP was made by combining two solutions at room temperature. Solution A contained 87.6 g calcium nitrate tetrahydrate in 624 mL of distilled water (pH 5.45). Solution B contained 203.7 g dibasic sodium phosphate heptahydrate and 100.0 g sodium bicarbonate in 2000 mL of distilled water. After mixing together for two minutes at room
- 15 temperature (pH 6.60), 42 mL of 10% wt/wt NaOH solution was added to the reaction mixture over 11 minutes to bring the pH to 7.29. The mixture was filtered by vacuum filtration (650 mL per funnel) and washed four times with 1000 mL of distilled water. After the last wash, the material was covered in liquid nitrogen and lyophilized for 24 hours. After
- 20 lyophilization, the powder was pushed through a 500  $\mu m$  sieve.

The resultant NCP powder was added to equal parts by weight dicalcium phosphate dihydrate (DCPD) as described in Example 5. The amount of  $H_2O$  added varied, depending on whether a thick or thin paste was desired. The paste material was then placed in a moist tissue

25 environment where upon reaching body temperature ( $37^\circ C$ ), it hardened into a solid mass. The hardening process could be delayed for several hours by placing it into a refrigerating temperature of  $4^\circ C$ .



Example 7. This example investigates the *in vitro* release kinetics of various calcium phosphate delivery materials.

The following materials were investigated for release of cisplatin.

Sample No.	Preparation according to:	Composition
5      1	Example 5; ground 10 minutes after mixing	50:50 ACP/DCPD
2	Example 5; ground 2 minutes after mixing	80:20 ACP/DCPD;
3	Example 6	50:50 NCP/DCPD
4	Example 1	ACP gel
5	Example 3	NCP gel
10    6	Example 2	ACP powder
7	Example 4	NCP powder

All materials were mixed together by hand. Since cisplatin is most stable in 0.9% sodium chloride, a 0.9% NaCl solution was used as both the hydrating agent for the powders and the medium into which cisplatin was released. See, Greene, et al. "Stability of Cisplatin in Aqueous Solutions," *American J. Hosp. Pharma.* 36:38 (1979). Release performance was determined by measuring cisplatin concentrations in supernatant liquid. Concentrations were determined by absorbance readings at 300 nm on a Shimadzu UV1601 UV-vis Spectrophotometer.

The most significant release of cisplatin took place in the first 24 hours for all materials tested. However, there were significant differences in the level of release that took place over this time, ranging from 35-75%. Changes in liquid to powder ratio were investigated, as well as sterile vs. non-sterile powders.

Figure 1 compares the release of cisplatin from sterile (◆) and non-sterile (■) powders of Sample 1. The plot indicates that the sterile material released a higher percentage of the cisplatin in the first 24 hours (ca 55%) than the non-sterile material (ca. 35%). This may be due to the differences in wetting abilities observed between the two materials.

Figure 2 compares the release of cisplatin from powders of Sample 1 (both non-sterile) having varying levels of added liquid. There is a significantly greater release of cisplatin from materials having a higher liquid load (◆) (ca. 70%) (1 g powder/0.9mL saline) than a similar material having a lower liquid load (■) (ca. 36%) (1 g powder/0.8 mL saline). This also represented the highest release of all the materials tested.

Figure 3A and 3B compare the release of cisplatin from NCP powder (Sample 7) that has been mixed with various levels of saline over 140 hours and 25 hours, respectively. The figures demonstrate that there is no significant difference in the extended release of cisplatin from NCP powder, whether it is mixed with excess saline (mixed wet) or not. However there is a difference in the initial release. Figure 3B demonstrates that NCP powder that has been mixed wet has a higher initial release rate than NCP powders that have not.

The two materials which released the most cisplatin over the first 24 hour period were sterile powders of Sample 1 mixed with a higher liquid content (liq/pow = 0.9) and NCP powder (Sample 7), regardless of liquid content, with approximately 73% and 65% released, respectively. From the foregoing, it is clear that in order to release the most cisplatin from Sample 1 material, the powders should be mixed wet. On the contrary, the level of saline used will not affect the total amount of cisplatin released from NCP material; however, it can be used to modify

the rate in initial release from the material. Thus, it can be seen that modifications of calcium phosphate composition and liquid load can have a significant effect on the release of the anticancer agent, thereby demonstrating that the release profile of the drug may be tailored to the specific needs of the user.

Example 8. This example demonstrates the effectiveness of the methods and materials of the invention in treating prostate cancer. The goal of this study was to use a calcium phosphate material as a delivery vehicle for cisplatin at a prostate cancer tumor site and to evaluate the effectiveness of cisplatin-calcium phosphate delivery system in treating AT2.1 rat prostate cancer tumors in athymic nude mice.

The model used for this study was the nude mouse having an immune system deficiency that allows for tumor growth. Dose calculations were based on human doses, mouse weights and body surface area calculation, as have been previously reported. See, Hawk, C.T. and Leary, S.L. Formulary for Lab Animals, 2<sup>nd</sup> Ed. Iowa State Press ( ) and Rozenzweig, et al. "Cis-diamminedichloride platinum(II): A New Anticancer Drug", *Annals Intern. Med.* 86:803 (1977).

The cell line for prostate cancer, AT-2, was chosen due to ease of access and previous studies indicating that cisplatin administered intravenously causes tumor inhibition. See, Teicher, et al., Anticancer Drug Development Guide. Humana Press, New Jersey (1997).

The decision of which calcium phosphate material to use was based upon release kinetic studies of cisplatin mixed with various calcium phosphate powders.

A protocol was established which included two materials based on Samples 1 and 7 of Example 6. The first material was selected to test treatment both inside and outside the tumor, while the second material was

selected to test two different dosage levels as well as treatment inside and outside the tumor. Table 3 includes the protocol used for the mice study (total of 40 athymic nude mice).

**Table 3.**

5	Group 1: Positive control (Dose 1 - 0.5 mg/0.2cc) n=2	
	Group 2: Positive control (Dose 2 - 0.25 mg/0.2 cc) n=2	
	Group 3: Negative control n=5 (no treatment)	
	Sample 1	Sample 7
10	Group 4: Dose 1 n=3 material alone inside tumor	Group 8: Dose 1 n=3 material alone inside tumor
	Group 5: Dose 1 n=3 material alone outside tumor	Group 9: Dose 1 n=3 material with cisplatin outside tumor
	Group 6: Dose 1 n=3 material with cisplatin inside tumor	Group 10: Dose 2 n=3 material alone inside tumor
15	Group 7: Dose 1 n=3 material with cisplatin outside tumor	Group 11: Dose 2 n=3 material with cisplatin inside tumor
	Group 12: Dose 1 n=3 material with cisplatin inside tumor	Group 13: Dose 1 n=3 material with cisplatin inside tumor

The mice were 5-6 week old male athymic nu/nu nude mice. They were housed in solid bottom mouse cages maintained within a semi-rigid isolator. They were fed a 23.5% protein, 6% fat autoclavable rodent laboratory chow fed ad-lib. Water was sterile filtered and provided in water bottles.

Mice were inoculated subcutaneously in the shoulder area with  $1 \times 10^6$  tumor cell in 0.1 mL of culture medium and 0.1 mL Matrigel. After two weeks, 0.2 cc of treatment or control materials or 0.5cc of positive control solutions were injected directly into the tumor. The positive control cisplatin solution was prepared by dissolving a specified amount

of cisplatin in sterile saline for injection through a 25 gauge needle directly into the tumor. The appropriate calcium phosphate delivery vehicle was supplied as a sterile powder in a preweighed package. At the time of injection, each powder was hydrated with the appropriate amount  
5 of saline and loaded into a 0.1 cc syringe for injection through a 16 gauge needle. Each material was mixed on site and immediately injected at the tumor site using a 1 cc syringe with a Luer-Lok® tip and a 16-gauge needle. At the study site, each animal was weighed and its tumor size was recorded, using hand-held calipers for the measurements.

10       The tumors had a blister-like appearance, but upon further investigation were actually solid and somewhat grainy to the touch and not fluid-filled. For some materials, the needle was inserted directly into the tumor, and was injected inside. In some cases, the material was observed coming out the other side of the tumor still underneath the skin.  
15 Therefore, it can be surmised that not all of the material was retained within the tumor. For the other materials, the needle was placed below the tumor and the material was injected alongside the tumor. As before, the material could be seen spreading somewhat below the skin and it was hard to determine exactly how much of the material was in contact with the  
20 tumor. The control solutions were also mixed on site and injected as described above.

Both materials injected easily. One syringe filled with material provided adequate volume for 2-3 mice; however, due to the warm body temperature of the mice, the material at the needle tip hardened between  
25 mice. This problem was solved by changing syringe needles between mice. The material in the syringe remained injectable for the duration of the procedure. The needle did leave a rather large hole in the mouse skin where inserted and it may be advisable to use an 18-gauge needle instead.

The material is mixed wet, i.e., at a higher liquid component load, and is therefore easily injectable. Liquid component load was adjusted to attain the desired consistency, as needed. The material was sufficiently flowable so as to be capable of injection using an 18-gauge needle.

- 5           Animals were monitored over a 20-day period for changes in body weight and tumor mass. Tumor shrinkage accompanied by the absence of toxic side effects (as determined by loss of body weight) was considered an indication of successful treatment.

- Figure 4 is a plot of the % tumor mass change over time for  
10   average of cisplatin plus Sample 1-treated animals (◆), average of negative control animals (■), and average of positive control animals (▲). Negative control animals, which received no chemotherapy, demonstrated rapid and excessive tumor growth. The animals were sacrificed on Day 7 due to excessive tumor load. The plot clearly demonstrates that the  
15   cisplatin locally delivered to the tumor in a calcium phosphate delivery vehicle based on ACP/DCPD matched the ability of intravenous delivery of cisplatin (positive control). Positive control animals, however, were sacrificed on Day 14 due to excessive weight loss.

- Figure 5 is a plot of animal body weight over time for average  
20   positive control animals (◆), and average cisplatin plus Sample 1-treated animals (■). The plot demonstrates a regular and consistent weight loss for positive control animals, up to about 50% of body mass by the time the animals were sacrificed at Day 14. In contrast, the cisplatin plus Sample 1-treated animals showed weight gain over the treatment course while at  
25   the same time showing no increase in tumor size. This demonstrates that the calcium phosphate materials of the invention have been successfully used in the treatment of prostate cancer tumors. The treatment was

effective for at least 20 days, the duration of the study, over which time the cisplatin plus ACP/DCPD-treated animals demonstrated no tumor growth and body mass gains.

Example 9. The goal of this study was to use a calcium phosphate material as a delivery vehicle for cisplatin at a mammary tumor site and to evaluate the effectiveness of cisplatin-calcium phosphate delivery system in treating MTGB Mouse cancer tumors in C3H mice.

A protocol was established to administer a two component calcium phosphate delivery vehicle using the material of Example 6 to a tumor interior. The material was tested at two different cisplatin dosage levels and compared against a systemically delivered control. Table 4 includes the protocol used for the mice study (total of 80 athymic nude mice).

**Table 4.**

	Group 1: Positive control (Dose 1 - 25 mg/kg IV systemic control); n=12
15	Group 2: Positive control (Dose 2 - 10 mg/kg IV systemic control); n=12
	Group 3: Negative control (no treatment); n=11
	Group 4: Dose 1 - 25 mg/kg 50:50 NCP/DCPD inside tumor; n=11
	Group 5: Dose 2 - 10 mg/kg 50:50 NCP/DCPD inside tumor; n=11
	Group 6: Negative control (50:50 NCP/DCPD only inside tumor); n=12

20 The mice were C3H mice (approx. 20 g). They were housed in solid bottom mouse cages maintained within a semi-rigid isolator. They were fed an 18% protein, 5% fat rodent laboratory chow fed ad-lib, gamma-irradiated prior to use. Water was sterile filtered and provided in water bottles. Ambient temperature is 72 degrees F +/- 5 degrees with a  
25 relative humidity of 50% +/- 20%.

Mice were inoculated subcutaneously in the flank area with  $1 \times 10^6$  tumor cell in 0.1 mL of RPMI culture medium. After tumors had grown to 8-10 mm, 0.1 cc of treatment or control materials (except for positive systemic controls which were administered by IV) were injected directly into the tumor with an 18-gauge needle. The positive control cisplatin solution was prepared by dissolving a specified amount of cisplatin in sterile saline for injection through a 25 gauge needle directly into the tumor. The appropriate calcium phosphate delivery vehicle was supplied as a sterile powder in a preweighed package. At the time of injection, each powder was hydrated with the appropriate amount of saline and loaded into a 0.1 cc syringe for injection through a 16 gauge needle. Each material was mixed on site and immediately injected at the tumor site using a 1 cc syringe with a Luer-Lok® tip and a 16-gauge needle. At the study site, each animal was weighed and its tumor size was recorded, using hand-held calipers for the measurements. Mice were sacrificed when tumor mass was greater than 10% of body weight.

Animals were monitored over a 20-day period for changes in body weight and tumor mass. Tumor shrinkage accompanied by the absence of toxic side effects (as determined by loss of body weight) was considered an indication of successful treatment.

Figure 6 is a plot of the % tumor mass change over time for 25 mg/kg cisplatin dose in calcium phosphate delivery vehicle (▲), calcium phosphate delivery vehicle alone (\*), no treatment (+), and systemic IV administration of 25 mg/kg cisplatin (-). As is clearly shown, negative control animals (curves (\*) and (+)), which received no chemotherapy, demonstrated rapid and excessive tumor growth. The animals were sacrificed on Day 7 due to excessive tumor load. The plot clearly demonstrates that the cisplatin locally delivered to the tumor in a calcium



- phosphate delivery vehicle based on NCP/DCPD matched the ability of intravenous delivery of cisplatin (positive control); however, positive control animals died on Day 5 due to excessive weight loss. See, Figure 7. Positive control animals, however, remained active and apparently healthy over the 20 day observation period.

**Example 10.** The goal of this study was to use a calcium phosphate material as a delivery vehicle for cisplatin at a prostate cancer tumor site and to evaluate the effectiveness of cisplatin-calcium phosphate delivery system in treating DU-145 human cancer tumors in nude mice.

- A protocol was established to administer a two component calcium phosphate delivery vehicle using the material of Example 6 to a tumor interior. The material was tested at two different cisplatin dosage levels and compared against a systemically delivered control. Table 5 includes the protocol used for the mice study (total of 36 NU/NU-nuBR nude mice).

**Table 5.**

	Group 1: Positive control (Dose 1 - 25 mg/kg IV systemic control); n=6
	Group 2: Positive control (Dose 2 - 10 mg/kg IV systemic control); n=6
	Group 3: Negative control (no treatment); n=6
20	Group 4: Dose 1 - 25 mg/kg 50:50 NCP/DCPD inside tumor; n=6
	Group 5: Dose 2 - 10 mg/kg 50:50 NCP/DCPD inside tumor; n=6
	Group 6: Negative control (50:50 NCP/DCPD only, inside tumor); n=6

- The mice were female 5-6 week old Crl:NU/NU-nuBR, which are nude outbred mice. mice (approx. 17-21 g). They were housed in solid bottom mouse cages maintained within a semi-rigid isolator. They were fed a 18% protein, 5% fat rodent laboratory chow fed ad-lib, gamma-

irradiated prior to use. Water was sterile filtered and provided in water bottles. Ambient temperature is 72 degrees F +/- 5 degrees with a relative humidity of 50% +/- 20%.

- Mice were inoculated subcutaneously in the flank area with 2 x 10<sup>6</sup> tumor cell in 0.1 mL of RPMI culture medium with 30% Matrigel. After tumors had grown to 100 ± 35 mg, 0.1 cc of treatment or control materials (except for positive systemic controls which were administered by IV) were injected directly into the tumor with an 18-gauge needle. The positive control cisplatin solution was prepared by dissolving a specified amount of cisplatin in sterile saline for injection through a 25 gauge needle directly into the tumor. The appropriate calcium phosphate delivery vehicle was supplied as a sterile powder in a preweighed package. At the time of injection, each powder was hydrated with the appropriate amount of saline and loaded into a 0.1 cc syringe for injection through a 16 gauge needle. Each material was mixed on site and immediately injected at the tumor site using a 1 cc syringe with a Luer-Lok® tip and a 16-gauge needle. At the study site, each animal was weighed and its tumor size was recorded, using hand-held calipers for the measurements. Mice were sacrificed when two consecutive tumor mass measurements greater than 1000 mg were recorded.

Animals were monitored over a 20-plus day period for changes in body weight and tumor mass. Tumor shrinkage accompanied by the absence of toxic side effects (as determined by loss of body weight) was considered an indication of successful treatment.

- Figure 8 is a plot of the % tumor mass change over time for (a) 25 mg/kg cisplatin dose in calcium phosphate delivery vehicle, (b) calcium phosphate delivery vehicle alone, (c) no treatment and (d) systemic IV administration of 25 mg/kg cisplatin. As is clearly shown, negative

control animals (curve (b)), which received no chemotherapy, demonstrated rapid and excessive tumor growth. The animals were sacrificed on Day 14 due to excessive tumor load. The plot clearly demonstrates that the cisplatin locally delivered to the tumor in a calcium  
5 phosphate delivery vehicle based on NCP/DCPD matched the ability of intravenous delivery of cisplatin (positive control) to contain tumor growth; however, positive control animals died on Day 4 due to excessive weight loss. See, Figure 7. Positive control animals, however, remained active and apparently healthy over the 21 day observation period.

10           What is claimed is:

1. A method for treating cancer in a mammal, said method comprising the step of:

administering to a tumor site of the mammal an anticancer composition comprising a mixture of an anticancer agent and a calcium phosphate paste, said paste comprised of one or more calcium phosphates and a physiologically acceptable fluid, the paste having an injectable or formable consistency at the time of administration and hardenable at the tumor site.

2. The method of claim 1, wherein each calcium phosphate has a Ca/P ratio of less than or equal to 1.7.

3. The method of claim 1, wherein the anticancer agent is selected from the group consisting of methotrexate, cis-platin, prednisone, hydroxyprogesterone, medroxyprogesterone acetate, megestrol acetate, diethylstilbestrol, testosterone propionate, fluoxymesterone, vinblastine, vincristine, vindesine, daunorubicin, doxorubicin, hydroxyurea, procarbazine, aminoglutethimide, mechlorethamine, cyclophosphamide, mephalan, uracil mustard, chlorambucil, busulfan, carmustine, lomusline, dacarbazine (DTIC, dimethyltriazenomideazolecarboxamide), fluorouracil, 5-fluorouracil, cytarabine, cytosine arabinoside, mercaptopurine, 6-mercaptopurine, tamoxifen, paclitaxel, etoposide, vinorelbine, gemcitabine, leuprolide, flutamide, goserelin acetate, and thioguanine, and mixtures thereof.

4. The method of claim 1, wherein the anticancer composition is administered to the tumor site by cannula or by injection.

5. The method of claim 4, wherein the anticancer composition is administerable by cannula or injection more than five minutes after its preparation.

6. The method of claim 4, wherein the anticancer composition is administerable by cannula or injection more than twenty minutes after its preparation.

7. The method of claim 1, wherein the paste hardens into an apatitic calcium phosphate.

8. The method of claim 1, wherein the calcium phosphate paste comprises a calcium phosphate selected from the group consisting of amorphous calcium phosphate, poorly crystalline apatitic (PCA) calcium phosphates (PCA), dicalcium phosphates, such as dicalcium phosphate dihydrate (DCPD) and dicalcium phosphate anhydrous (DCPA), tricalcium phosphates (TCP), monetite, monocalcium phosphate monohydrate (MCPM), hetpocalcium phosphate, calcium pyrophosphate, calcium metaphosphate, octacalcium phosphates (OCP), hydroxyapatites (HA).

9. The method of claim 8, wherein at least one of the calcium phosphates is selected from the group consisting of amorphous calcium phosphate and poorly crystalline apatitic calcium phosphate.

10. The method of claim 1, wherein each of the said one or more calcium phosphates has a calcium to phosphate ratio in the range of 1.0 to 1.67.
11. The method of claim 1 wherein each of the said one or more  
5 calcium phosphates has a calcium to phosphate ratio in the range of 1.3 to 1.67.
12. The method of claim 1 wherein the calcium phosphate paste has an overall calcium to phosphate ratio in the range of 1.0 to 1.7.
13. The method of claim 1, wherein the calcium phosphate paste  
10 has an overall calcium to phosphate ratio in the range of 1.40 to 1.65.
14. The method of claim 1, wherein calcium phosphate paste comprises a physiologically acceptable fluid in an amount sufficient to produce a paste having injectable or formable consistency.
15. The method of claim 1, wherein a therapeutically effect  
15 amount of anticancer agent is released from the composition for a time greater than one week.
16. The method of claim 1, wherein a therapeutically effect amount of anticancer agent is released from the composition for a time greater than two week.

17. The method of claim 1, wherein a therapeutically effect amount of anticancer agent is released from the composition for a time greater than one month.
18. The method of claim 1, wherein a therapeutically effect  
5 amount of anticancer agent is released from the composition for a time greater than three months.
19. The method of claim 1, wherein delivery of the anticancer therapy to the tumor site is sufficient to prevent increase of tumor mass  
10 without significant weight loss of the mammal.
20. The method of claim 1, wherein delivery of the anticancer therapy to the tumor site is sufficient to result in a decrease in tumor mass without significant weight loss in the mammal.
21. The method of claim 1, wherein the particle size of the calcium  
15 phosphate is selected to provide a desired release kinetic of the anticancer drug.
22. A composition for treating cancer, said composition comprising a mixture of a physiologically effective amount of an anticancer agent and a calcium phosphate paste, said paste comprised of  
20 one or more calcium phosphates and a physiologically acceptable fluid, the paste having an injectable or formable consistency at the time of administration and hardenable at the tumor site.

23. The composition of claim 22, wherein each calcium phosphate has a Ca/P ratio of less than or equal to 1.7.

24. The composition of claim 22, wherein the anticancer agent is selected from the group consisting of methotrexate, cis-platin, prednisone, hydroxyprogesterone, medroxyprogesterone acetate, megestrol acetate, diethylstilbestrol, testosterone propionate, fluoxymesterone, vinblastine, vincristine, vindesine, daunorubicin, doxorubicin, hydroxyurea, procarbazine, aminoglutethimide, mechlorethamine, cyclophosphamide, mephalan, uracil mustard, chlorambucil, busulfan, carmustine, lomusline, dacarbazine (DTIC, dimethyltriazenomideazolecaboxamide), fluorouracil, 5-fluorouracil, cytarabine, cytosine arabinoside, mercaptopurine, 6-mercaptopurine, tamoxifen, paclitaxel, etoposide, vinorelbine, gemcitabine, leuprolide, flutamide, goserelin acetate, and thioguanine, and mixtures thereof.
25. The composition of claim 22, wherein the anticancer composition is of a consistency administerable to the tumor site by cannula or by injection.



26. The composition of claim 22, wherein the calcium phosphate cement comprises a calcium phosphate selected from the group consisting of amorphous calcium phosphate, poorly crystalline apatitic (PCA) calcium phosphates (PCA), dicalcium phosphates, such as dicalcium phosphate dihydrate (DCPD) and dicalcium phosphate anhydrous (DCPA), tricalcium phosphates (TCP), monetite, monocalcium phosphate monohydrate (MCPM), heptacalcium phosphate, calcium pyrophosphate, calcium metaphosphate, octacalcium phosphates (OCP), hydroxyapatites (HA).
- 10 27. The composition of claim 26, wherein at least one of the calcium phosphates is selected from the group consisting of amorphous calcium phosphate and poorly crystalline apatitic calcium phosphate.
28. The composition of claim 22, wherein each of the said one or more calcium phosphates has a calcium to phosphate ratio in the range of  
15 1.3 to 1.67.
29. The composition of claim 22, wherein the calcium phosphate paste has an overall calcium to phosphate ratio in the range of 1.0 to 1.7.
30. The composition of claim 22, wherein the calcium phosphate paste has an overall calcium to phosphate ratio in the range of 1.0 to 1.67.
- 20 31. The composition of claim 22, wherein the calcium phosphate paste has an overall calcium to phosphate ratio in the range of 1.40 to 1.65.

32. The composition of claim 22, wherein calcium phosphate paste comprises a physiologically acceptable fluid in an amount sufficient to produce a paste having injectable or formable consistency for at least five minutes.
- 5           33. The composition of claim 22, wherein calcium phosphate paste comprises a physiologically acceptable fluid in an amount sufficient to produce a paste having injectable or formable consistency for at least twenty minutes.
34. The composition of claim 22, wherein the calcium phosphate  
10 paste is hardenable into an apatitic calcium phosphate.
35. The composition of claim 22, wherein a therapeutically effect amount of anticancer agent is released from the composition for a time greater than one week.
- 15           36. The composition of claim 22, wherein a therapeutically effect amount of anticancer agent is released from the composition for a time greater than two week.
37. The composition of claim 22, wherein a therapeutically effect amount of anticancer agent is released from the composition for a time  
20 greater than one month.
38. The composition of claim 22, wherein a therapeutically effect amount of anticancer agent is released from the composition for a time greater than three months.

39. The composition of claim 22, wherein delivery of the anticancer therapy to the tumor site is sufficient to at least prevent increase of tumor mass without significant weight loss of the mammal.

5           40. The composition of claim 22, wherein delivery of the anticancer therapy to the tumor site is sufficient to prevent a decrease in tumor mass without significant weight loss in the mammal.

41. The composition of claim 22, wherein the particle size of the calcium phosphate is selected to provide a desired release kinetic of the  
10 anticancer drug.

42. A kit for use in preparing a flowable anticancer composition that remain injectable for at least about 20 minutes, said kit comprising:  
dry ingredients comprising amorphous calcium phosphate and a second calcium phosphate in a proportion of about 1:10 to 10:1 by weight;  
15 a physiologically acceptable aqueous lubricant in an amount sufficient to produce a flowable product upon combination with said dry ingredients; and  
an anticancer agent in an amount ranging from about 0.01 to 10 wt. % of said dry ingredients.

20           43. The kit of claim 42, further comprising a means of mixing the dry ingredients and the lubricant.

44. The kit of claim 42, further comprising injecting means.

45. A method for making a medicament for treating cancer in a mammal, said method comprising mixing a physiologically effective amount of an anticancer agent and a calcium phosphate paste, said paste comprised of one or more calcium phosphates and a physiologically acceptable fluid, the paste having an injectable or formable consistency at the time of administration and hardenable at the tumor site.

46. The method of claim 45, wherein each calcium phosphate has a Ca/P ratio of less than or equal to 1.7.

47. The method of claim 45, wherein the anticancer agent is selected from the group consisting of methotrexate, cis-platin, prednisone, hydroxyprogesterone, medroxyprogesterone acetate, megestrol acetate, diethylstilbestrol, testosterone propionate, fluoxymesterone, vinblastine, vincristine, vindesine, daunorubicin, doxorubicin, hydroxyurea, procarbazine, aminoglutethimide, mechlorethamine, cyclophosphamide, mephalan, uracil mustard, chlorambucil, busulfan, carmustine, lomusline, dacarbazine (DTIC, dimethyltriazenomideazolecarboxamide), fluorouracil, 5-fluorouracil, cytarabine, cytosine arabinoside, mercaptopurine, 6-mercaptopurine, tamoxifen, paclitaxel, etoposide, vinorelbine, gemcitabine, leuprolide, flutamide, goserelin acetate, and thioguanine, and mixtures thereof.

48. The method of claim 45, wherein the anticancer composition is of a consistency administerable to the tumor site by cannula or by injection.

49. The method of claim 45, wherein the calcium phosphate cement comprises a calcium phosphate selected from the group consisting of amorphous calcium phosphate, poorly crystalline apatitic (PCA) calcium phosphates (PCA), dicalcium phosphates, such as dicalcium phosphate dihydrate (DCPD) and dicalcium phosphate anhydrous (DCPA), tricalcium phosphates (TCP), monetite, monocalcium phosphate monohydrate (MCPM), heptacalcium phosphate, calcium pyrophosphate, calcium metaphosphate, octacalcium phosphates (OCP), hydroxyapatites (HA).
- 10        50. The method of claim 45, wherein at least one of the calcium phosphates is selected from the group consisting of amorphous calcium phosphate and poorly crystalline apatitic calcium phosphate.
- 15        51. The method of claim 45, wherein each of the said one or more calcium phosphates has a calcium to phosphate ratio in the range of 1.3 to 1.67.
52. The method of claim 45; wherein the calcium phosphate paste has an overall calcium to phosphate ratio in the range of 1.0 to 1.7.
53. The method of claim 45, wherein the calcium phosphate paste has an overall calcium to phosphate ratio in the range of 1.0 to 1.67.
- 20        54. The method of claim 45, wherein the calcium phosphate paste has an overall calcium to phosphate ratio in the range of 1.40 to 1.65.

55. The method of claim 45, wherein calcium phosphate paste comprises a physiologically acceptable fluid in an amount sufficient to produce a paste having injectable or formable consistency for at least five minutes.
- 5        56. The method of claim 45, wherein calcium phosphate paste comprises a physiologically acceptable fluid in an amount sufficient to produce a paste having injectable or formable consistency for at least twenty minutes.
57. The method of claim 45, wherein the calcium phosphate paste  
10 is hardenable into an apatitic calcium phosphate.
58. The method of claim 45, wherein a therapeutically effect amount of anticancer agent is released from the composition for a time greater than one week.
- 15        59. The method of claim 45, wherein a therapeutically effect amount of anticancer agent is released from the composition for a time greater than two week.
60. The method of claim 45, wherein a therapeutically effect amount of anticancer agent is released from the composition for a time  
20 greater than one month.
61. The method of claim 45, wherein a therapeutically effect amount of anticancer agent is released from the composition for a time greater than three months.

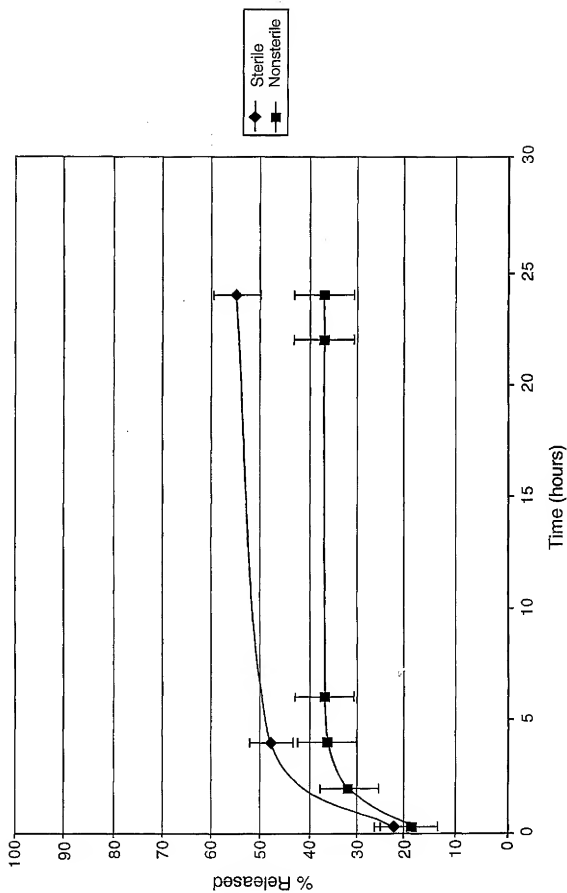
62. The method of claim 45, wherein delivery of the anticancer therapy to the tumor site is sufficient to at least prevent increase of tumor mass without significant weight loss of the mammal.

63. The method of claim 45, wherein delivery of the anticancer  
5 therapy to the tumor site is sufficient to prevent a decrease in tumor mass without significant weight loss in the mammal.

64. The method of claim 45, wherein the particle size of the calcium phosphate is selected to provide a desired release kinetic of the anticancer drug.

1/10

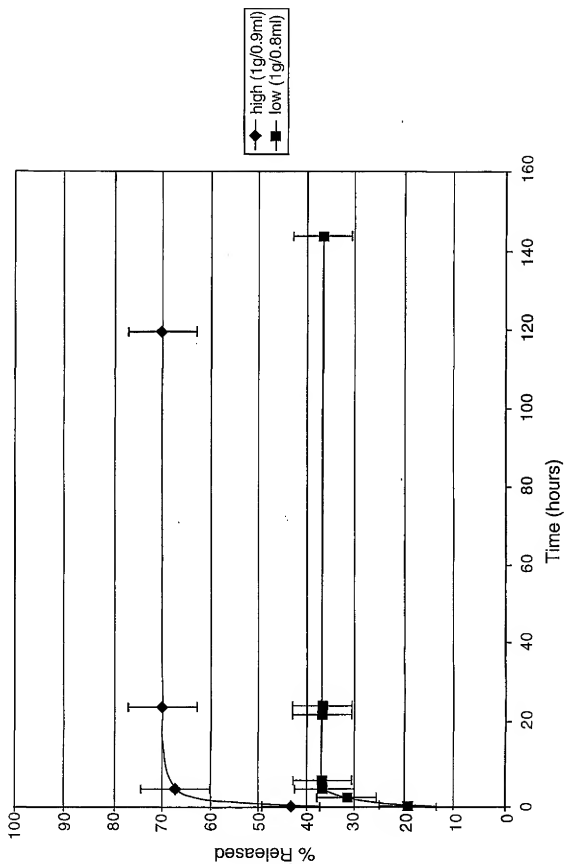
FIG. 1





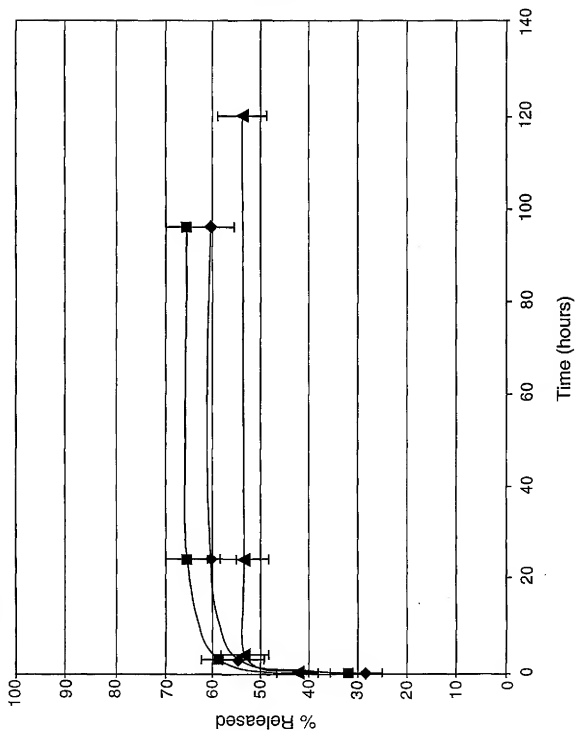
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FIG. 2



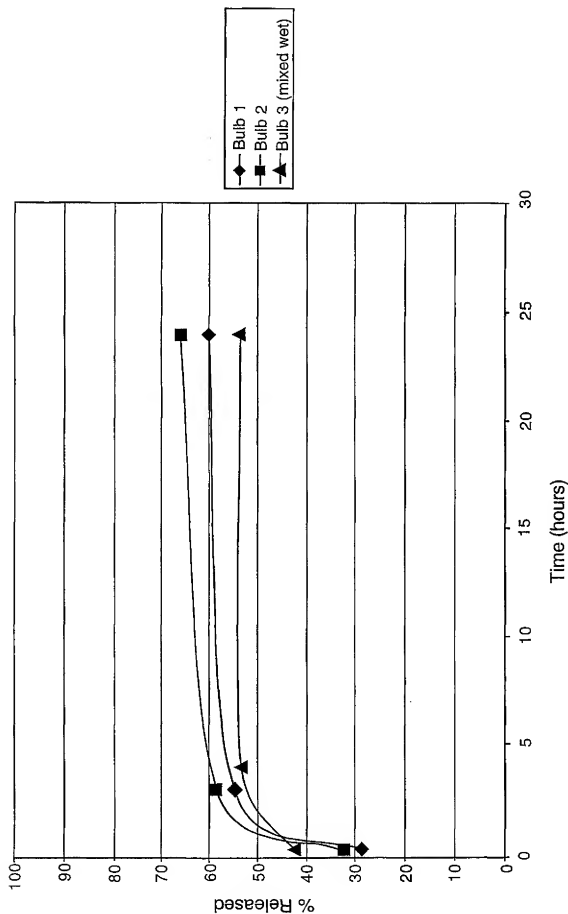
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FIG. 3A

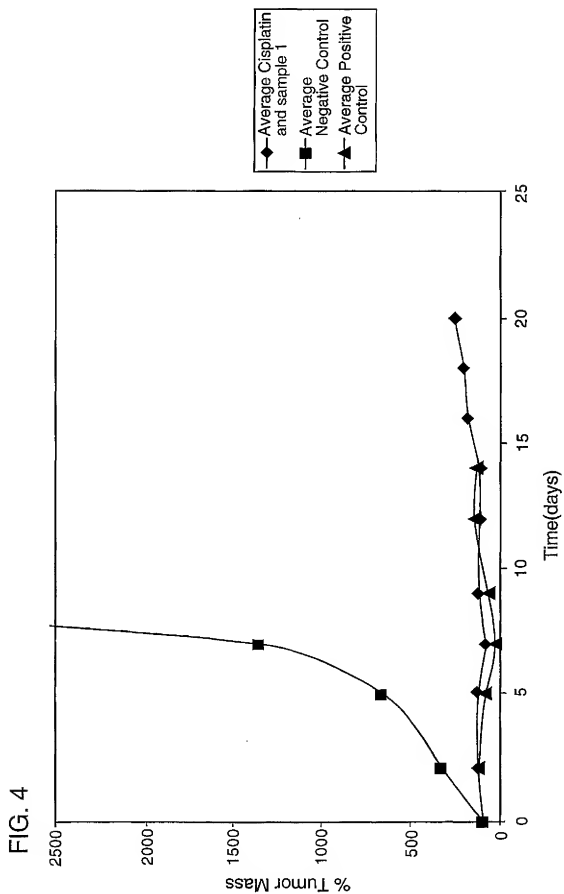


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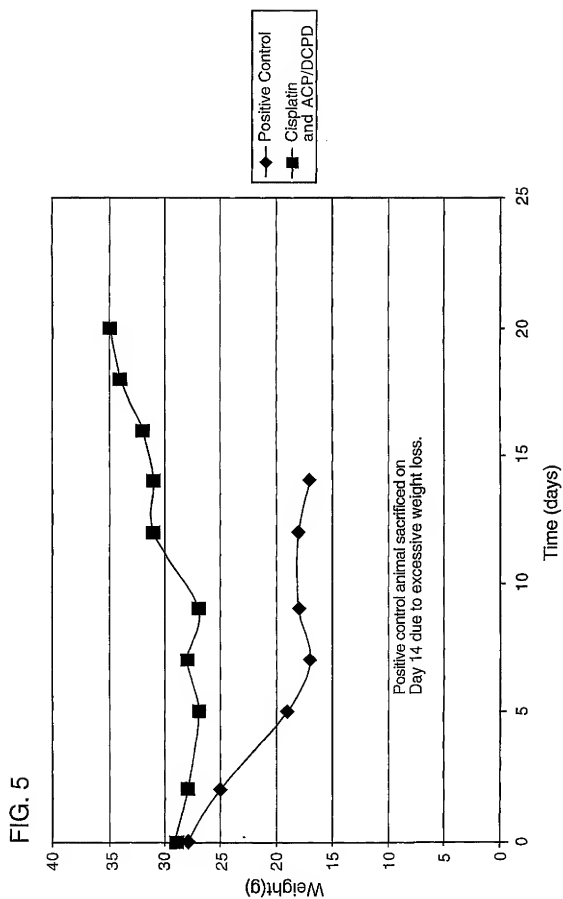
FIG. 3B



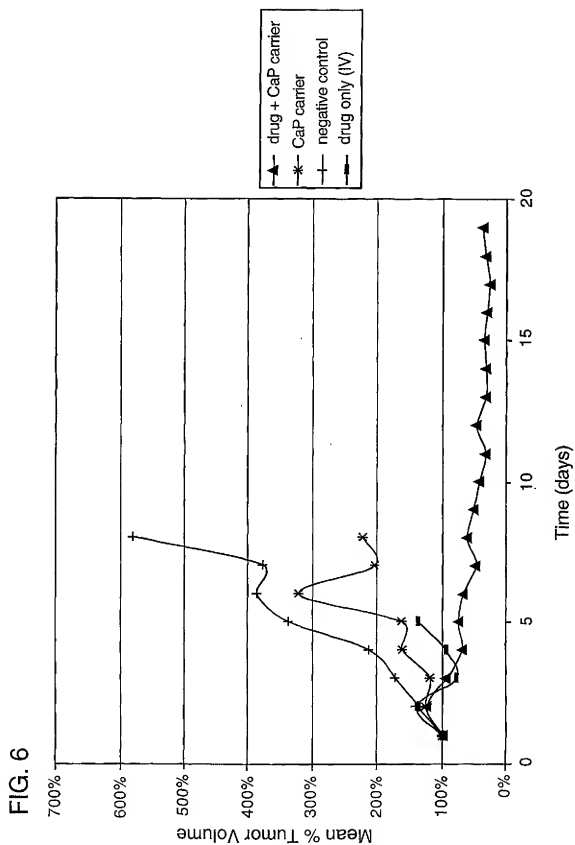
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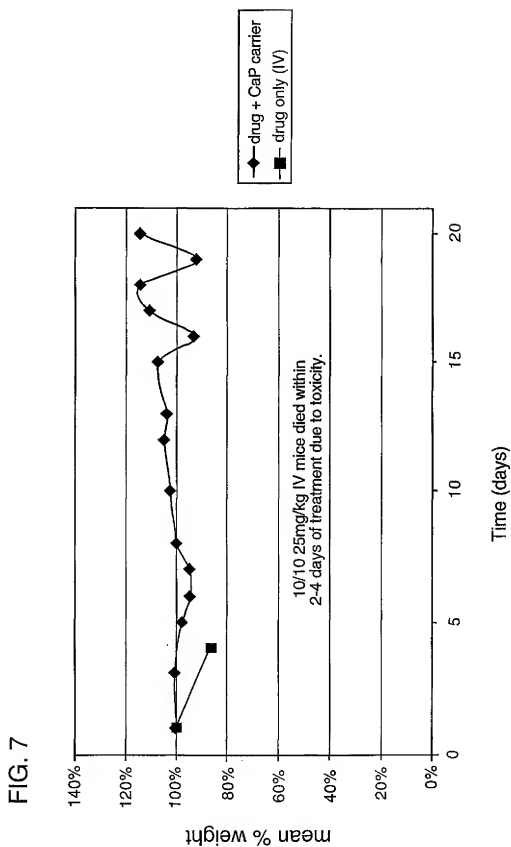
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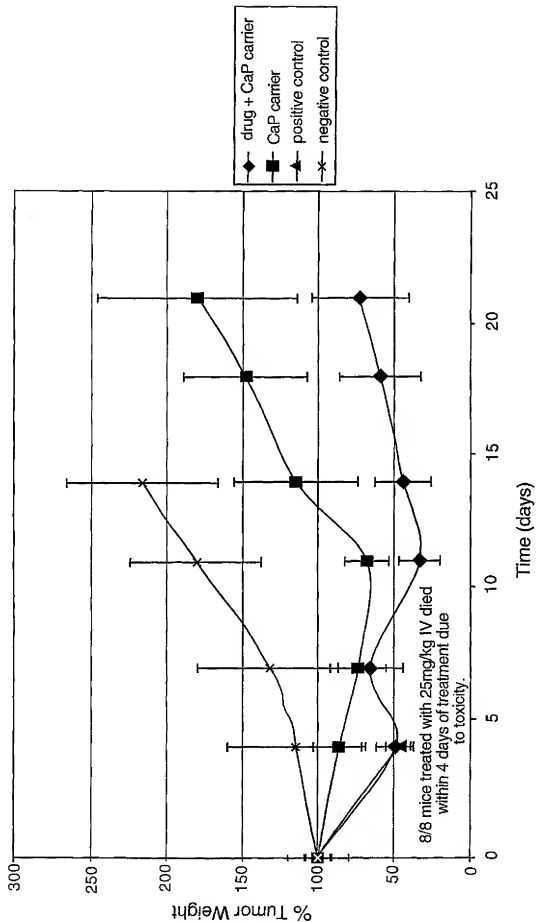


8/10



9/10

FIG. 8





10/10

FIG. 9

